PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 05 May 2000 (05.05.00)	
International application No. PCT/EP99/06290	**Applicant's or agent's file reference** 51622BWOM1XXOO-P
International filing date (day/month/year) 26 August 1999 (26.08.99)	**Priority date** (day/month/year) 28 August 1998 (28.08.98)
Applicant URICH, Klaus	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

14 March 2000 (14.03.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer

Claudio Borton

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

SCHERING AKTIENGESELLSCHAFT
D-13342 Berlin
ALLEMAGNE

Date of mailing (day/month/year) 06 June 2000 (06.06.00)	
Applicant's or agent's file reference 51622BWOM1XXOO-P	**IMPORTANT NOTIFICATION**
International application No. PCT/EP99/06290	**International filing date** (day/month/year) 26 August 1999 (26.08.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
SCHERING AKTIENGESELLSCHAFT Müllerstrasse 178 D-13353 Berlin Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
SCHERING AKTIENGESELLSCHAFT D-13342 Berlin Germany	DE	DE
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
New address for correspondence.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer Athina Nickitas-Etienne
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

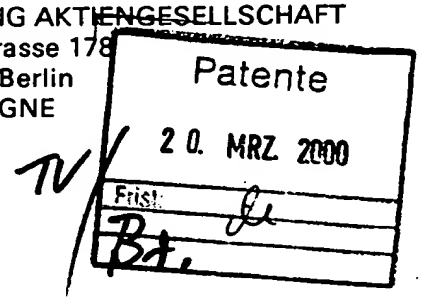
From the INTERNATIONAL BUREAU

PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

To:
SCHERING AKTIENGESELLSCHAFT
Müllerstrasse 178
D-13353 Berlin
ALLEMAGNE



Date of mailing (day/month/year) 09 March 2000 (09.03.00)	
Applicant's or agent's file reference 516228WOM1XXOO-P	**IMPORTANT NOTICE**

International application No.	**International filing date** (day/month/year)	**Priority date** (day/month/year)
PCT/EP99/06290	26 August 1999 (26.08.99)	28 August 1998 (28.08.98)

Applicant
SCHERING AKTIENGESELLSCHAFT et al

1. Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:
   AU,CN,EP,JP,KP,KR,US

   In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

2. The following designated Offices have waived the requirement for such a communication at this time:
   AE,AL,AM,AP,AT,AZ,BA,BB,BG,BR,BY,CA,CH,CR,CU,CZ,DK,DM,EA,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,KE,KG,KZ,LC,LK,LR,LS,LT,LU,LV,MD,MG,MK,MN,MW,MX,NO,NZ,OA,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TR,TT,UA,UG,UZ,VN,YU,ZA,ZW
   The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

3. Enclosed with this Notice is a copy of the international application as published by the International Bureau on
   09 March 2000 (09.03.00) under No. WO 00/12158

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a demand for international preliminary examination must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the national phase, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No. (41-22) 740.14.35

Authorized officer
J. Zahra

Telephone No. (41-22) 338.83.38

Continuation of Form PCT/IB/308

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

Date of mailing (day/month/year)	IMPORTANT NOTICE
09 March 2000 (09.03.00)	
Applicant's or agent's file reference	**International application No.**
51622BWOM1XXOO-P	PCT/EP99/06290

The applicant is hereby notified that, at the time of establishment of this Notice, the time limit under Rule 46.1 for making amendments under Article 19 has not yet expired and the International Bureau had received neither such amendments nor a declaration that the applicant does not wish to make amendments.

PATENT COOPERATION TREATY

SZ 22-146623

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PRÜFER & PARTNER
Harthauser Strasse 25d
D-81545 München
ALLEMAGNE

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	29.11.2000
Applicant's or agent's file reference 51622AWOM1XX00-P Br/	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06290	26/08/1999	28/08/1998

Applicant
SCHERING AKTIENGESELLSCHAFT et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Terzic, K Tel.+49 89 2399-2052

Form PCT/IPEA/416 (July 1992)

15

PATENT COOPERATION TREATY

REC'D 04 DEC 2000

WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
51622AWOM1XX00-P Br/		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/06290	26/08/1999	28/08/1998

International Patent Classification (IPC) or national classification and IPC
A61M5/145

Applicant
SCHERING AKTIENGESELLSCHAFT et al.

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
14/03/2000	29.11.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Rosenblatt, T Telephone No. +49 89 2399 8732

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/06290

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-15 as originally filed

Claims, No.:

1-33 as originally filed

Drawings, sheets:

1/6-6/6 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7,11,12,15-33
	No:	Claims	1-6,8-10,13,14
Inventive step (IS)	Yes:	Claims	
	No:	Claims	7,11,12,15-33
Industrial applicability (IA)	Yes:	Claims	1-33
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

   D1: US-A-4 687 000 (EISENHARDT ANNE R ET AL) 18 August 1987 (1987-08-18)
   D2: US-A-5 352 036 (HABER TERRY M ET AL) 4 October 1994 (1994-10-04)
   D3: US-A-3 789 670 (ROSENWALD G) 5 February 1974 (1974-02-05)
   D4: DE 296 22 313 U (TRICUMED GMBH) 6 March 1997 (1997-03-06)
   D5: US-A-3 880 138 (WOOTTEN JOHN A ET AL) 29 April 1975 (1975-04-29)

2.1 Document D1 shows in figure 3 the following features of claim 1:

a syringe suitable for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

- a body (10) comprising a distal discharge end;
- a plunger (11) movably disposed within the body;
- one agitation element (15) disposed within the body between the plunger and the distal discharge end, the agitation element operable to agitate a fluid in the syringe, when the syringe is moved with respect to gravity by means of the movement mechanism operably associated with the injector (col. 3, lines 26 to 34).

Since all features of claim 1 are known from D1, claim 1 lacks novelty (Art. 33(2) PCT.

2.2 The subject-matter of claim 1 lacks also novelty in view of documents D2 and D4. The cartridge shown in fig. 3 of D3, although not at all referring to the intended use as a syringe with an injector, shows all technical features of claim 1 and can not be distinguished from this. Therefore claim 1 also lacks novelty in view of D3.

3. Dependent claims 2-4, 6, 8-10 do not define any additional technical features of the syringe (cf. paragraph VIII-2. below). The known syringes are suitable to be

used with the respective referred features, so that the syringes according to these dependent claims lack novelty.

4. The subject-matter of claim 5 is known from documents D1 to D4.

5. The subject-matter of claim 7 is not considered as inventive (Art. 33(3) PCT), becasue the feature **gas** is an equivalent to the feature **solid** of document D1 to D4 and can be interchanged with that feature where circumstances make it desirable.

6. In claims 11 and 12 slight constructional changes in the syringes of respective claims 1 and 7 are defined which come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of claims 11 and 12 also lacks an inventive step.

7. The subject-matter of claims 13 and 14 is known from document D3 (see Fig. 2).

8. In claim 15 and 16 slight constructional changes in the syringe of claim 1 are defined which come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of claims 15 and 16 also lacks an inventive step.

9. Claim 17 relates to an injector system such as known from document D5. The injector system of D5 includes a movement mechanism permitting longitudinal and rotational movement of the syringe assembly (col. 3, lines 3-8). The difference between the known injector system of D5 and the subject-matter of claim 1 is the agitation element disposed within the body between the plunger and the distal discharge end.

   The problem to be solved by this differentiating feature may be formulated as maintaining the homogeneity of the liquid to be injected.

   Feature **agitation element** is described in document D1 as providing the same

advantages as in the present application. The skilled person would therefore regard it as a normal design option to include this feature in the injector system described in document D5 in order to solve the problem posed.

Consequently the subject-matter of claim 17 lacks an inventive step (Art. 33(3) PCT).

10. Claims 18-20 and 22 do not define any additional technical features of the injector system (cf. paragraph VIII-2. below). The known injector system is suitable to be used with the respective referred features, so that the injector system according to these dependent claims lack novelty.

11. The subject-matter of claims 21 is known from D1 and the subject-matter of claims 24 and 25 is known from D1 and D5, so that these claims also lack an inventive step.

12. Claims 26 to 31 relate to slight constructional changes in the injector system of claim 17 which come within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen. Consequently, the subject-matter of these claims also lacks an inventive step.

13. Independent method claim 32 does not comply with the requirement of inventive activity as set forth in Art. 33(3) PCT, since a combination of the teachings of documents D1 and D5 would have been obvious for the skilled person. The reasons are equivalent to those presented for the lack-of-inventive-step objection concerning claim 17 under paragraph 9 here above.

14. No inventive acitivity can be seen in the additional step defined in claim 33, since terminating the agitation comes within the scope of the customary practice followed by persons skilled in the art, especially as the advantages thus achieved can readily be foreseen.

15. The devices and method according to claims 1 to 33 are susceptible of industrial application (Art. 33(4) PCT).

Re Item VII

Certain defects in the international application

1. The indepenedent claims 1 and 32 are not in two-part form as required by Rule 6.3(b) PCT.

2. The features of the claims are not provided with reference signs placed in parentheses (Rule 6.2(b) PCT).

3. Claim 17 contains all the features of claim 1 and should therefore have been formulated as a dependent claim (Rule 6.4(a) PCT).

4. The prior art syringes and injector system known from documents D1, D2, D4 and D5 should have been acknowledged in the description (Rule 5.1(a)ii) PCT).

Re Item VIII

Certain observations on the international application

1. Concerning the expression **syringe for use with...** employed in claim 1, the applicant is referred to the PCT Guidelines Section IV-III-4.8, PCT Gazette from 29.10.1998. Accordingly the above expression is construed as **syringe suitable for use with...** It is also considered that neither the fluid nor the movement mechanism are technical features of the syringe. Furthermore, the term **syringe** is interpreted in the broad sense given on page 6, second paragraph.

2. Dependent Claims 2-4, 6, 8-10, 18-20, 22 lack clarity in the sense of Art. 6 PCT. They all refer to features which have not been defined as features of the syringe of claim 1 or of the injector system of claim 17. In particular the subject-matter of claims 2, 3, 18 and 19 relates to properties of the fluid, which fluid has however not been defined as a feature of the syringe or injector system. The subject-matter of claims 4, 6, 20 and 22 defines features of the syringe by reference to features of the use (PCT Guidelines Section IV-III-4.8a) which introduces a lack of clarity. The density of the used fluid is not known a priori, so that the extent of protection cannot be determined. In claims 8-10 features of the movement mechanism are defined, although the movement mechanism is not a feature of the syringe.

3. The subject-matter of claim 26 does not appear supported by the description (Art. 6 PCT), since none of the embodiments shows the defined feature.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61M 5/145, B01F 11/00

A1

(11) International Publication Number: **WO 00/12158**

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(21) International Application Number: PCT/EP99/06290

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(30) Priority Data:
198 40 532.4 28 August 1998 (28.08.98) DE

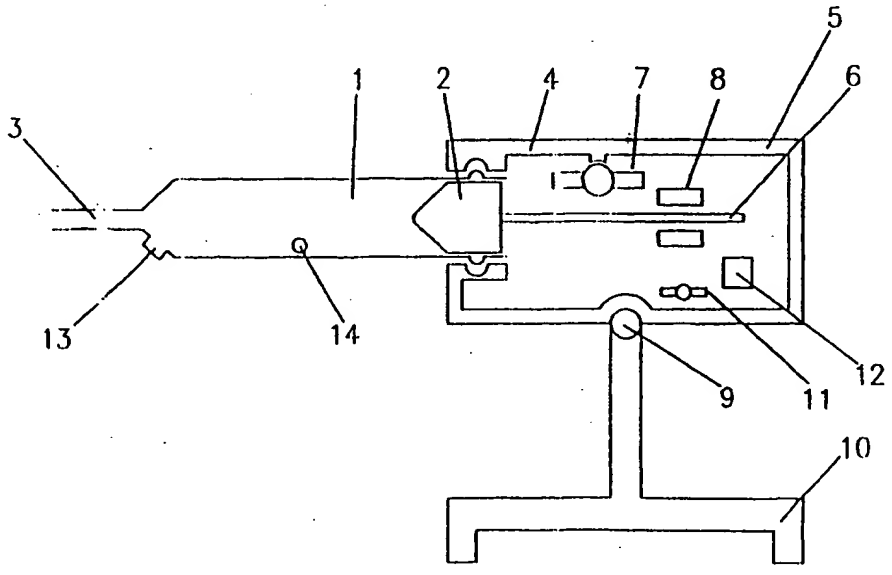
(71) Applicant *(for all designated States except US)*: SCHERING AKTIENGESELLSCHAFT [DE/DE]; Müllerstrasse 178, D–13353 Berlin (DE).

(72) Inventor; and
(75) Inventor/Applicant *(for US only)*: URICH, Klaus [DE/DE]; Parkstrasse 27a, D–13129 Berlin (DE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SYRINGES AND INJECTORS INCORPORATING MECHANICAL FLUID AGITATION DEVICES



(57) Abstract

A syringe for use with an injector includes a body comprising a distal discharge end, a plunger movably disposed within the body, and an agitation element disposed within the body between the plunger and the distal discharge end. A movement mechanism is operably associated with the injector to move the syringe in such a way that the at least one agitation element agitates a fluid contained in the syringe. Preferably, the syringe contains an ultrasound contrast agent that is agitated by the agitation element. An injector system and a method for agitating the contents of a syringe are also provided.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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SYRINGES AND INJECTORS INCORPORATING MECHANICAL FLUID AGITATION DEVICES

Background of the Invention

The present invention relates generally to movement devices for agitating the contents of syringes and, more particularly, to syringes and injectors incorporating movement devices for agitating contrast agents disposed within the syringes.

Syringes which are prefilled with ultrasound contrast agents are clamped into injectors for injection. The syringes remain therein for several minutes to one or more hours. The duration of one or more injections, including the intervening periods between the injections, may last for more than 10 minutes. Depending on the nature and composition of the contrast agent, dissociation commences at different times. During this period, the ultrasound contrast agent becomes dissociated and the phases are separated from one another. The ultrasound contrast agent as a whole is no longer homogeneous. In order to restore this homogeneity, the entire injector, including the syringe clamped therein, is moved manually. Movements of this nature are not reproducible, and sufficient homogenization is not ensured.

Ultrasound contrast agents are sensitive to transverse forces. Under excessively high forces, the particles are torn apart and destroyed. This impairs the quality of the ultrasound contrast agent. Thus, to maintain the suspension of particles in ultrasound contrast agents it is necessary to agitate the agents, but at the same time the particles must not be destroyed by the agitation.

Ultrasound contrast agents are generally described in Supplement to Diagnostic Imaging, May 1995, Advanced Ultrasound, Editor: Peter L. OGLE, Editorial Offices: 600 Harrison St. San Francisco, CA 94107 USA.

Glass syringes and plastic syringes are described extensively in the publication by Junga (M. JUNGA (1973) Pharm. Ind. Vol. 35, No. IIa, pages 824 to 829). A mixture of glass and plastic is described in PCT Publication No. WO 96/00098.

Injectors are generally described in EP Publication No. 0 584 531.

Summary of the Invention

The present invention provides apparatuses and methods for maintaining the homogeneity and integrity of an ultrasound contrast agent over a relatively long period of time without destroying the consistency of the ultrasound contrast agent and hence impairing its pharmacological and diagnostic properties. The dissociation begins immediately after the initial preparation of the ultrasound contrast agent, and at the latest after the syringe has been inserted into the injector when the latter is at rest (i.e., is not moving). By maintaining the homogeneity and integrity of the particles suspended in the contrast agent at optimal levels, the diagnostic properties of the contrast agent can be optimized.

The present invention further provides apparatuses and methods for continuous, controlled and/or reproducible agitation procedures for contrast agents. These procedures can be utilized between the time of preparation of the contrast agents and their injection into a patient.

Further, the present invention provides agitation procedures that can be specifically designed and/or adjusted for specific contrast agents, including ultrasound contrast agents.

Also, the agitation procedures may be designed to minimize turbulent agitation of the contrast agents, thereby reducing shear forces and other stresses that could be harmful to the integrity of the particles suspended in the contrast agents.

Moreover, the present invention provides a controlled application of magnetic energy to maintain the homogeneity of the contrast agent suspension, without mixing or otherwise destroying the particles of the contrast agents.

One aspect of the present invention is achieved by means of a syringe which is filled with ultrasound contrast agent for administering the contents thereof by means of an injector, wherein at least one agitation element is contained in the syringe. The agitation element can be present as a solid or a gas, and preferably has a different density from that of the ultrasound contrast agent. Preferably, the syringe is movable with respect to the lines of gravity by means of the injector or an accessory thereto.

Another aspect of the present invention is achieved by means of an injector, or an accessory therefore, that moves a syringe mounted thereon for inducing at least one agitation element disposed within the syringe to agitate the contents thereof. The at least one agitation element may be present in the syringe in a solid or a gas phase, and preferably has a density different from that of the ultrasound contrast agent.

In a preferred embodiment, the movements of the syringe are circular, partially circular or linear. The movements of the syringe must be such that the agitation element disposed within the syringe moves with respect thereto. Typical movements contemplated by the present invention include pitching, swaying, yawing and shaking. All linear movements with a horizontal vector are also included. Movements along the lines of gravity typically do not induce any mixing or homogenization of the contrast agent contained within the syringe. Only when a movement component which does not run exclusively along the lines of gravity is added does homogenization of the contrast agent become possible. Preferably, the movements are rotational movements, the axis of rotation of which may be arranged as desired.

In a preferred embodiment, the present invention provides a combination of a syringe filled with a contrast agent and an injector or an accessory for use with an injector. At least one agitation element is contained in the syringe, is present as a gas or a solid and has a density different from that of the contrast fluid. The syringe is movable with respect to the lines of gravity by means of the injector or the accessory therefore.

Preferably, the syringes are made from plastic, glass or plastic/glass. Furthermore, the syringe are preferably disposable syringes.

The agitation element may be a gas or a solid body, the density of which differs from that of the ultrasound contrast agent. Preferably, the agitation element comprises a solid body with a density that is higher than that of the ultrasound contrast agent. The agitation element can move in the syringe under the force of gravity, by the syringe being moved about, for example, one of its axes.

To accomplish this movement, the injector adjusts and/or moves the syringe by means of a tilting movement with respect to the longitudinal axis thereof. Preferably, the injector is mounted in such a way that the mounted, approximately horizontally-arranged syringe is moved about this position, the center of rotation preferably lying outside the syringe and the axis of rotation being perpendicular to the longitudinal axis of the syringe.

The present invention, along with further aspects and attendant advantages, will best be understood by reference to the following detailed description taken in conjunction with the accompanying drawings.

Brief Description of the Drawings

Figure 1 is an elevated, cross-sectional view of an injector system incorporating a rotation device between the injector stand and the injector housing.

Figure 2 is an elevated, cross-sectional view of an injector system incorporating an accessory for tilting the injector and syringe mounted thereon.

Figure 3 is a graphical view comparing the Doppler signal intensity of a contrast agent with resuspension versus that of the contrast agent with no resuspension.

Figure 4 is a graphical view comparing the Doppler signal intensity of a contrast agent with resuspension versus that of the contrast agent with no resuspension.

Figure 5 is a graphical view comparing the Doppler signal intensity of a contrast agent with no resuspension versus that of the contrast agent with low-speed and high-speed resuspensions.

Figure 6 is a graphical view comparing the Doppler signal intensity of a contrast agent with medium vibratory resuspension versus that of the contrast agent with no resuspension.

Detailed Description of the Presently Preferred Embodiments

Before turning to a detailed description of the preferred embodiments, as illustrated in Figures 1 and 2, the present invention is described first below in general terms applicable to all suitable embodiments thereof.

As an initial matter, the terms "syringe" and/or "syringes" as used herein can mean and encompass the following terms and devices: cartridges (large-volume syringe with a volume of at least 100 ml); ampoule syringes; disposable syringes; disposable syringe ampoules; throw-away syringe ampoules; throw-away syringes; injection ampoules; disposable injection ampoules; ready-for-injection ampoules; cylindrical ampoules; twin-chamber injection ampoules; two-chamber syringes; two-chamber syringe ampoules; and no-delay syringes.

In addition, the terms "injector" and/or "injectors" as used herein can mean and encompass the following terms and devices: infusion pumps; infusers; perfusors; and all other applicators or devices that operate to empty syringes of fluid contain therein.

Further, the terms "accessory" and/or "accessories" as used herein can mean and encompass the following: all devices which are or may be physically connected to an injector and assume the role of moving the entire injector or parts thereof in such a way that the syringe changes position. Typical accessories include tables which execute a wobbling movement or a rocking movement and on which the injectors are positioned. Further accessories may include a shaft, for example, a motor-drive shaft, that is attached to the stand of the injector and changes the position of the syringe. In this case, the syringe, a holder for the syringe, the ram and the ram-moving device (e.g., a motor) are usually rigidly connected to one another. The essential factor is that the injector or the accessory therefor moves at least the syringe with respect to the standing surface or suspension mount of the injector or of the accessory.

In the present invention, the agitation element may be encased by various substances. Suitable substances for the casing include, but are not limited to, glass and plastic materials, such as Teflon, which are preferably inert with respect to contrast agents. The use of a casing also reduces friction, which results in a reduction in or avoidance of particles within the syringe. Preferably, the agitation element is in the form of a ball. It is also possible for the gas to be surrounded by a cover, as is found with floats or immersed bodies.

The syringe preferably includes a recess therein for accommodating the agitation element. The recess preferably is designed in such a way that the agitation element can slide into or out of the recess. The recess preferably lies outside the movement range of the plunger in the syringe or itself forms part of the plunger.

Also, the recess may be formed both in the syringe and in the plunger. Preferably, the recess is positioned at or adjacent to the distal end (i.e., the syringe end having the needle attachment, hose attachment or luer lock fitting) of the syringe.

Further, the recess may be situated in the distal cover of the syringe cylinder or located in the syringe cylinder itself, close to the cover. In this case, a lock is preferably included to prevent the agitation element from blocking the syringe outlet.

In addition, the recess may comprise an annular recess that is disposed in the cover of the syringe cylinder. This design eliminates the need to orient the agitation element with respect to the syringe when the latter has been completely emptied.

Preferably, the recess is arranged in the syringe plunger. In this case, careful attention should be paid to the accurate orientation of the plunger with respect to the magnetic field source, unless an annular recess is situated in that part of the plunger which faces toward the needle attachment end (i.e.,

distal end) of the syringe. Combinations of recesses on the plunger and, at the same time, at that end of the syringe which lies at the needle attachment are also conceivable.

An important feature of the syringe is the design of the plunger, the closure, and the corresponding distal opening.

The agitation element must be controlled in such a way that sufficient homogenization is ensured but the particles in the ultrasound contrast agent are not destroyed by transverse forces. The intensity and frequency of the movement has to be controlled, in accordance with the sensitivity of the ultrasound contrast agent and in accordance with the movement sequence, in such a way that the consistency of the particles in the ultrasound contrast agent is not adversely affected.

Turning now to the drawings of the preferred embodiments, Figure 1 illustrates a syringe 1 having a plunger 2 movably disposed therein and a needle attachment or distal discharge end 3. The syringe 1 is removably connected to an injector 5 via a holder 4. Therefore, the syringe 1 can be inserted into the holder 4 in a reversible manner.

The injector 5 has a ram 6 which is removably connected to the plunger 2 of the syringe 1. The ram 6 is moved with respect to the housing of the injector 5 by a motor 7, the motor turning a ring 8 which has a screw thread and surrounds the ram 6, which likewise has a complementary screw thread. The ring 8 is rotatable with respect to the housing.

The housing of the injector 5 is connected to the stand 10 of the injector 5 via a joint 9. A rocker motor 11 allows relative movement between housing of the injector 5 and its stand 10. The movement of the rocker motor 11 is controlled by a control device 12. It is possible here to account individually for the nature of the contrast agent, the size of the syringe, the volume per minute of the injection and the stress of the patient.

At or near the distal end of the syringe 1, the syringe 1 includes a recess 13 for accommodating an agitation element 14, which is preferably in the form of a ball. Shortly before the syringe 1 has been completely emptied of its contents, the control device 12 adjusts the position of the syringe 1 in such a way that the ball 14 slides into the recess 13, thereby allowing the plunger 2 to be driven completely to the end of the syringe 1 in the direction of the needle attachment end 3 thereof.

Figure 2 illustrates a syringe 1 having a plunger 2 movably disposed therein and a needle attachment or distal discharge end 3. The syringe 1 is removably connected to an injector 5 via a holder 4. Therefore, the syringe 1 can be inserted into the holder 4 in a reversible manner.

The injector 5 includes a ram 6 which is removably connected to the plunger 2 of the syringe 1. The ram 6 is moved with respect to the housing of the injector 5 by a motor 7, the motor turning a ring 8 which has a screw thread and surrounds the ram 6, which likewise has a complementary screw thread. The ring 8 is rotatable with respect to the housing.

The injector 5, as shown, preferably stands on an accessory 15 for the injector. This accessory 15 has a stand base 16 and a stand surface 17 which is connected to the stand base 16 via a pivot joint 18. A lifting motor 19 moves a linkage 20 which is designed in the form of scissors and is connected to the motor via a connecting rod 21. The movement is controlled by means of a control device 12.

In the end of the plunger 2 facing the distal discharge end 3 of the syringe 1, the plunger 2 includes a plunger recess 22 for accommodating an agitation element 14, which is preferably in the form of a ball. Shortly before the syringe 1 has been completely emptied of its contents, the control device 12 adjusts the position of the syringe 1 in such a way that the ball 14 slides into the

plunger recess 22, thereby allowing the plunger 2 to be driven completely in the direction of the needle attachment 3 end thereof.

Examples

Example 1

A vibratory agitator was used to prevent phase separation in Levovist™ ultrasound contrast agent. The vibratory agitator includes a motor-driven vibrating unit and an electronic control unit containing a battery supply and controls for regulating the degree of vibration. The vibrating unit was connected mechanically to the syringe.

At low concentrations (e.g., 200 mg/ml), Levovist™ does not remain stable as a suspension for longer than 2-3 minutes. The suspension separates into two different phases: a liquid phase (which forms on the top of the agent) and a particle phase (which collects at the bottom). After resuspension, however, Levovist™ still provides optimal clinical results.

At a concentration of 300 mg/ml, Levovist™ separates into phases after 25-30 minutes, well above the Levovist™ approval limit of 10-15 minutes. At a concentration of 400 mg/ml, Levovist™ separates only after a matter of hours. Thus, for concentrations of 300 mg/ml and 400 mg/ml, no additional agitation is required to maintain Levovist™ in solution.

Test Setup

The vibratory agitator was tested with a 200 mg/ml concentration of Levovist™ using in-vitro Doppler measurement equipment. An IVAC P400 pump and a 20-ml Levovist™ syringe, which was connected directly to the vibratory agitator. To avoid vibration power loss, the pump's syringe holder was not connected to the syringe.

Testing Method

The trial consisted of three separate examinations without vibration and three with medium vibration power. The infusion flow settings were between 100 and 200 ml/h. Different flow settings only lead to differences ion the achievable Doppler intensity, not to differences in the (qualitative) curve form.

Test Results

Figure 6 illustrates the results of the tests in graphical form, which plots Doppler intensity (dB) versus time (Sec.). The graph in Figure 6 shows (1) three trials without vibration; and (2) three trials with a constant medium vibration.

Without vibration, the typical suspension problems with Levovist™ at a concentration of 200 mg/ml are shown in Figure 6. It is not possible to obtain a constant plateau phase of Doppler intensity. All of the non-vibration curves have more than one local maximum over time. Curve 3 does have a plateau, but only for one minute and at a low intensity level.

With vibration, plateau phases were achieved for the following durations: (1) Curve 1 – 2 minutes (70-190 sec.); (2) Curve 2 – 1.5 minutes (90-180 sec.); and (3) Curve 3 – 3 minutes (120-300 sec.).

However, the vibratory agitator did not provide a complete constant Doppler intensity plateau. In the vibratory curves, a second maximum with too strong an increase in Doppler intensity was observed. For example, second maximums occurred at the following times: (1) Curve 1 – at 300 sec. and at plus 10dB compared to the prior level; (2) Curve 2 – at 200 sec. and at plus 8dB compared to the prior level; and (3) Curve 3 – at 350 sec. and at plus 14dB compared to the prior level.

Example 2

The below examples use magnetic bars and ferromagnetic balls driven by a magnetic field to agitate or resuspend the contrast agents. While the examples do not use the mechanical devices disclosed herein, the results of increased and/or consistent enhancement properties for agitated or resuspended contrast agents may be considered independent of the means used to agitate or resuspend the contrast agents.

For Levovist™ 200 mg/ml ultrasound contrast fluid, which is manufactured by Schering AG of Berlin, Germany, phase separation occurs within a couple of minutes (approximately 3-5 minutes) after preparation. This phase separation is characterized by contrast particles aggregating at the lower part of a syringe containing the contrast fluid and the watery diluent collecting above the contrast particles within the syringe.

A number of technical approaches to mitigating and/or preventing Levovist™ phase separation were tested using a standardized laboratory model. In the first technical approach, a small ferromagnetic ball (having a higher specific weight then Levovist™) was placed in a syringe and moved therein by means of a magnetic field applied thereto. In the second technical approach, an agitation element (having a higher specific weight then Levovist™) was placed in the syringe and moved therein by means of an external magnetic bar moved outside of and relative to the syringe.

Test Setup

The tests were conducted using in-vitro test equipment validated to simulate in-vivo contrast enhancement conditions. The test equipment allowed reproducible measurements of the enhancement characteristics of ultrasound contrast fluid suspensions.

Through the controlled movement or control of a magnetic field source, agitation elements placed in the syringe were able to be moved in a

controlled fashion to agitate the ultrasound contrast fluid to prevent phase separation. After agitation, the ultrasound contrast fluid was injected into the testing equipment using a transfer tube and a 22G needle. The simulated body temperature was 37°C and the simulated negative pressure of the lung simulating component (i.e., oxygenator) of the testing equipment was 100 mBar.

Testing Method

Respective measurements of the enhancement properties of the ultrasound contrast fluid suspension over a prolonged period of time (up to 22 minutes) were conducted for syringes having magnetic agitation elements and for syringes not incorporating magnetic agitation elements. A standard infusion / injection speed of 1 ml/min was used throughout the tests. The impact of the phase separation mitigation approaches were deducted from the variances in the measured Doppler-signal intensity.

Test Results – Test One

As shown in Figure 3, no agitation of the ultrasound contrast fluid suspension leads to significant unfavorable inconsistencies in the enhancement properties of the contrast fluid, which is not suitable for clinical applications. However, when a magnetic bar was used to agitate the ultrasound contrast fluid suspension within the syringe, by means of a magnetic source located outside of the syringe, the contrast fluid was resuspended and a long-lasting, stable enhancement pattern was achieved.

Test Results – Test Two

In this test, a ferromagnetic ball was moved within the syringe through application of an outside magnetic field. Again, as shown in Figure 4, the test results clearly indicate that resuspension of the ultrasound contrast fluid suspension leads to significantly more consistent enhancement properties when compared to non-resuspended ultrasound contrast fluid suspension. With

regard to the non-resuspended contrast fluid enhancement properties, the differences compared to Results – Test One (above) show that the extent and impact of phase separation on contrast enhancement is largely unpredictable.

Test Results – Test Three

In this test, a magnetic bar was moved within the syringe through application of a ferromagnetic object outside the syringe. Besides a baseline comparison (i.e., compared to no resuspension of contrast fluid suspension), the influence of variations in the strength of the mechanical forces for resuspension were investigated. As can be clearly deducted from the test results, as shown in Figure 5, ultrasound contrast fluid suspensions contain fragile particles and the mechanical forces applied for resuspension must therefore be adjusted to the stability and strength of the contrast fluid suspension. An extremely vigorous resuspension is detrimental for the enhancement properties of the contrast fluid, whereas a slight agitation may not prevent phase separation. The key is to adjust the resuspension mode in way that the forces impacting the contrast fluid particles do not impair or limit their contrast enhancement purpose. The level of mechanical force required and/or tolerable for each individual ultrasound contrast fluid, including Levovist™ varies, but a reproducible and controllable resuspension mode is required.

It should be appreciated that the present invention may be configured as appropriate for the application. The embodiments described above are to be considered in all respects only as illustrative and not restrictive. The scope of the invention is indicated by the following claims, rather than by the foregoing description. All changes which fall within the meaning and range of equivalency of the claims are to be embraced within their scope.

List of reference numerals:

1 Syringe
2 Plunger
3 Needle attachment
4 Holder
5 Injector
6 Ram
7 Motor
8 Ring
9 Joint
10 Stand foot
11 Rocker motor
12 Control device
13 Bulge
14 Ball
15 Accessory
16 Stand base
17 Stand surface
18 Pivot joint
19 Lifting motor
20 Linkage
21 Connecting rod
22 Plunger bulge

WHAT IS CLAIMED IS:

1. A syringe for use with an injector having a movement mechanism operably associated therewith, the syringe comprising:

a body comprising a distal discharge end;

a plunger movably disposed within the body; and

at least one agitation element disposed within the body between the plunger and the distal discharge end, the at least one agitation element operable to agitate a fluid in the syringe when the syringe is moved with respect to gravity by means of the movement mechanism operably associated with the injector.

2. The syringe of Claim 1 wherein the fluid comprises a contrast agent.

3. The syringe of Claim 2 wherein the contrast agent comprises an ultrasound contrast agent.

4. The syringe of Claim 1 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

5. The syringe of Claim 1 wherein the at least one agitation element comprises a solid.

6. The syringe of Claim 5 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

7. The syringe of Claim 1 wherein the at least one agitation element comprises a gas.

8. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in one or more of circular, partially circular and linear motions.

9. The syringe of Claim 1 wherein the movement mechanism operably associated with the injector is operable to move the syringe in a rotational motion.

10. The syringe of Claim 9 wherein the axis of rotation is variable.

11. The syringe of Claim 1 wherein the at least one agitation element comprises a casing.

12. The syringe of Claim 7 wherein the at least one agitation element is surrounded by a cover.

13. The syringe of Claim 1, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

14. The syringe of Claim 13 wherein the recess is defined adjacent to the distal discharge end of the syringe.

15. The syringe of Claim 1, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

16. The syringe of Claims 13-15 wherein the recess comprises an annular recess.

17. An injector system comprising:

an injector comprising means for mounting a syringe thereon;

a syringe comprising a body having a distal discharge end and means cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end; and

a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe.

18. The injector system of Claim 17 wherein the fluid comprises a contrast agent.

19. The injector system of Claim 18 wherein the contrast agent comprises an ultrasound contrast agent.

20. The injector system of Claim 17 wherein the at least one agitation element has a density different from that of the fluid contained within the syringe.

21. The injector system of Claim 17 wherein the at least one agitation element comprises a solid.

22. The injector system of Claim 21 wherein the at least one agitation element has a density greater than that of the fluid in the syringe.

23. The injector system of Claim 17 wherein the at least one agitation element comprises a gas.

24. The injector system of Claim 17 wherein the movement mechanism moves the syringe in one or more of circular, partially circular and linear motions.

25. The injector system of Claim 17 wherein the movement mechanism moves the syringe in a rotational motion.

26. The injector system of Claim 25 wherein the axis of rotation is variable.

27. The injector system of Claim 23 wherein the at least one agitation element is surrounded by a cover.

28. The injector system of Claim 17, further comprising a recess defined in the body of the syringe, the recess operable to accommodate the at least one agitation element.

29. The injector system of Claim 28 wherein the recess is defined adjacent to the distal discharge end of the syringe.

30. The injector system of Claim 17, further comprising a recess defined in the plunger of the syringe, the recess operable to accommodate the at least one agitation element.

31. The injector system of Claims 28-30 wherein the recess comprises an annular recess.

32. A method for agitating the contents of a syringe, comprising:

providing an injector comprising means for mounting a syringe thereon;

providing a syringe comprising a body having a distal discharge end and means cooperable with the injector means for mounting the syringe on the injector, a plunger movably disposed within the body, and at least one agitation element disposed within the body between the plunger and the distal discharge end;

providing a movement mechanism operably associated with the injector, the movement mechanism operable to move the syringe such that the at least one agitation element agitates a fluid contained in the syringe;

activating the movement mechanism to move the syringe; and

agitating the fluid in the syringe with the at least one agitation element.

33. The method of Claim 32, further comprising the step of deactivating the movement mechanism to terminate the agitation of the syringe contents.

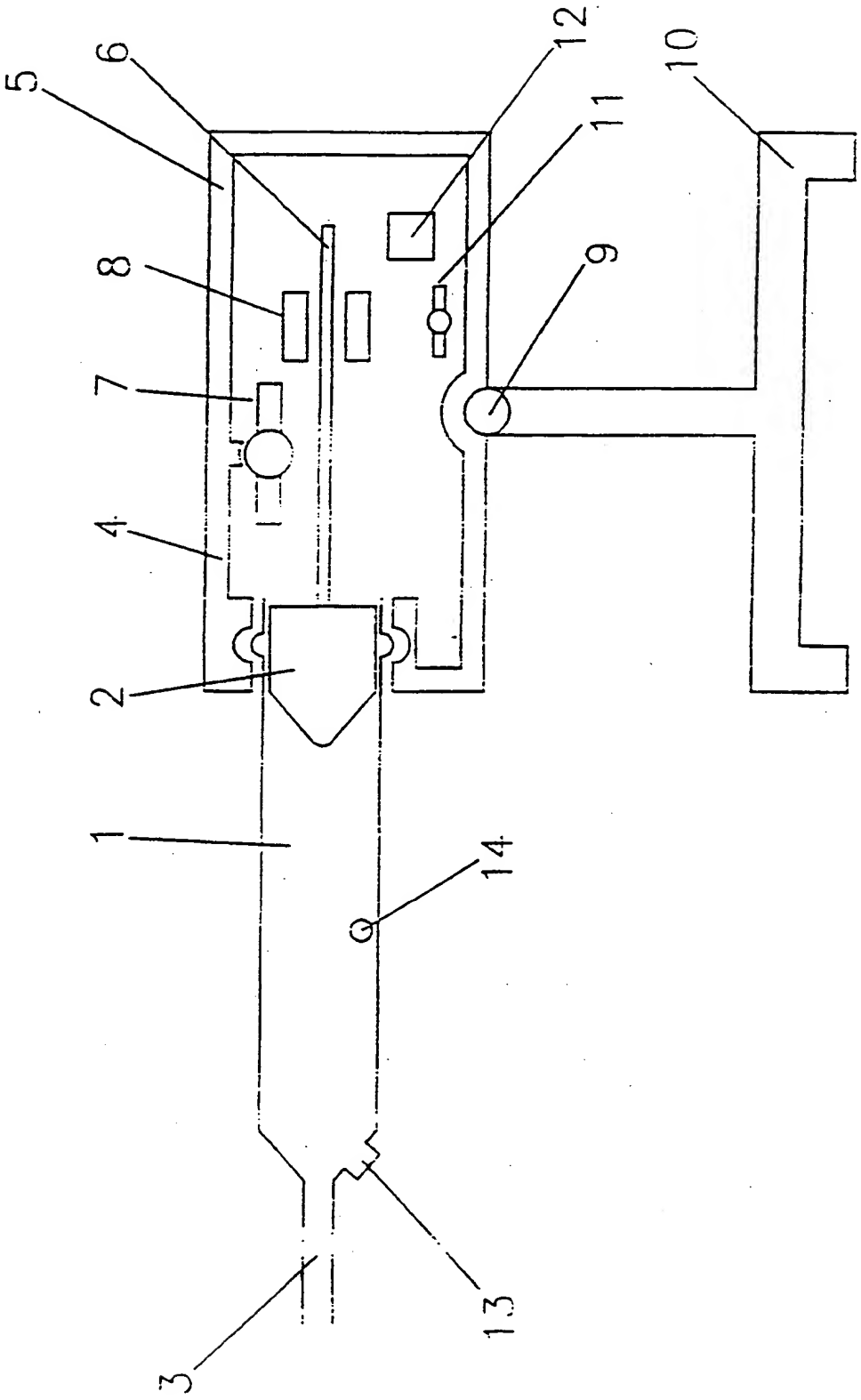


Figure 1

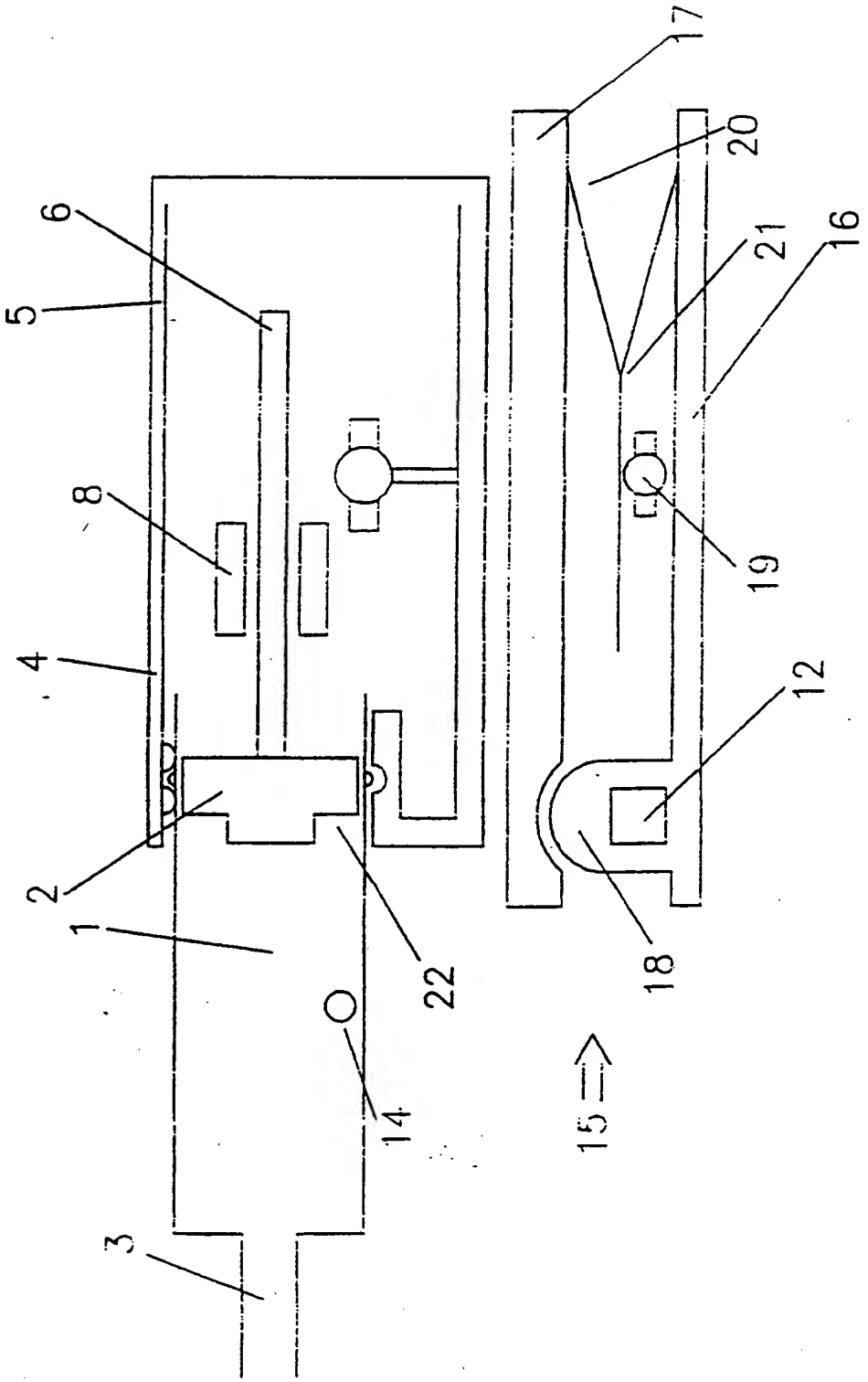
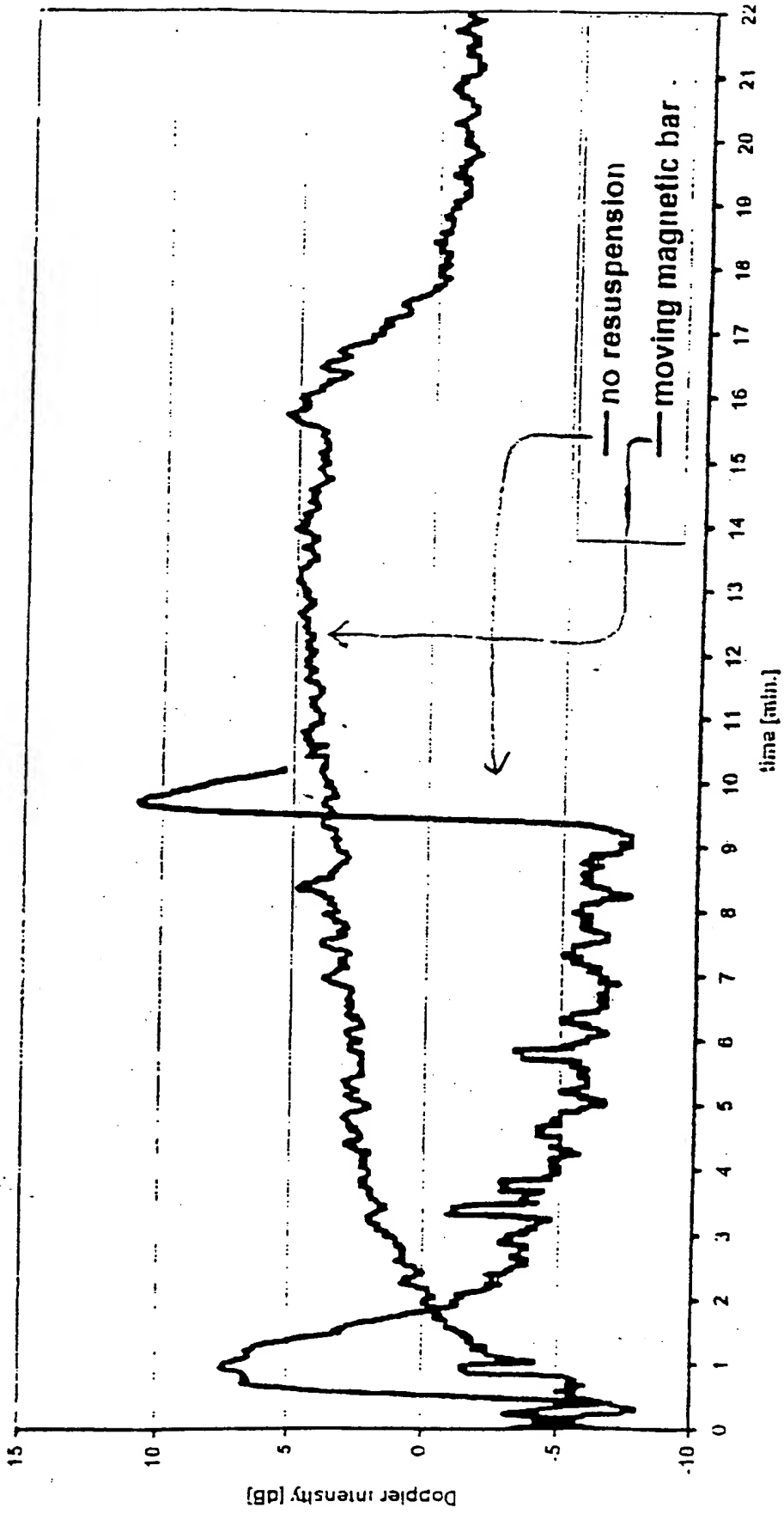


Figure 2


no resuspension
moving magnetic bar
time [min.]
Doppler intensity [dB]
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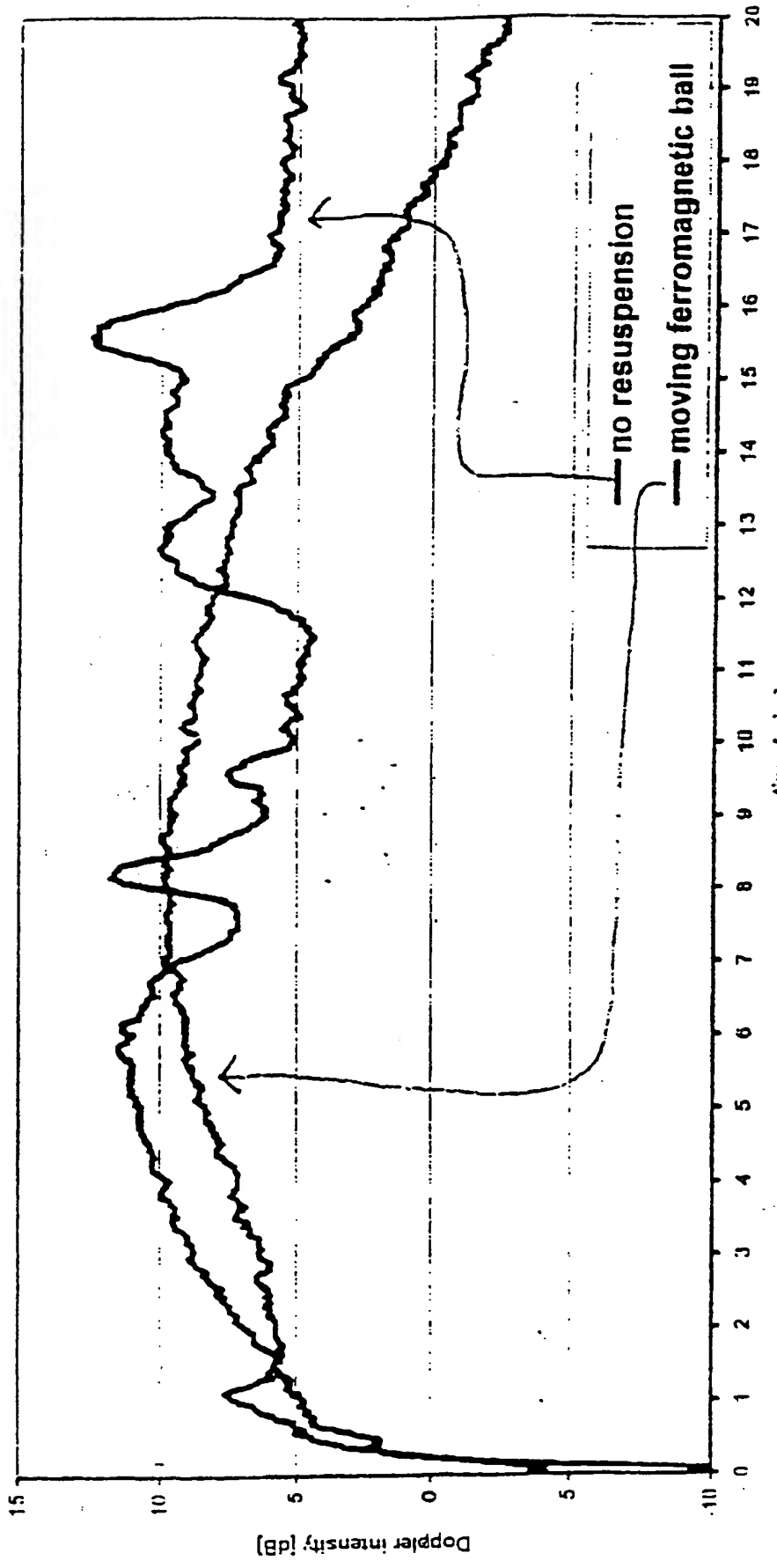
10
5
0
-5
-10
0
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22

Figure 3


no resuspension
moving ferromagnetic ball
time [min.]
Doppler intensity [dB]
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10
5
0
5
10
0
1
2
3
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5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20

Figure 4

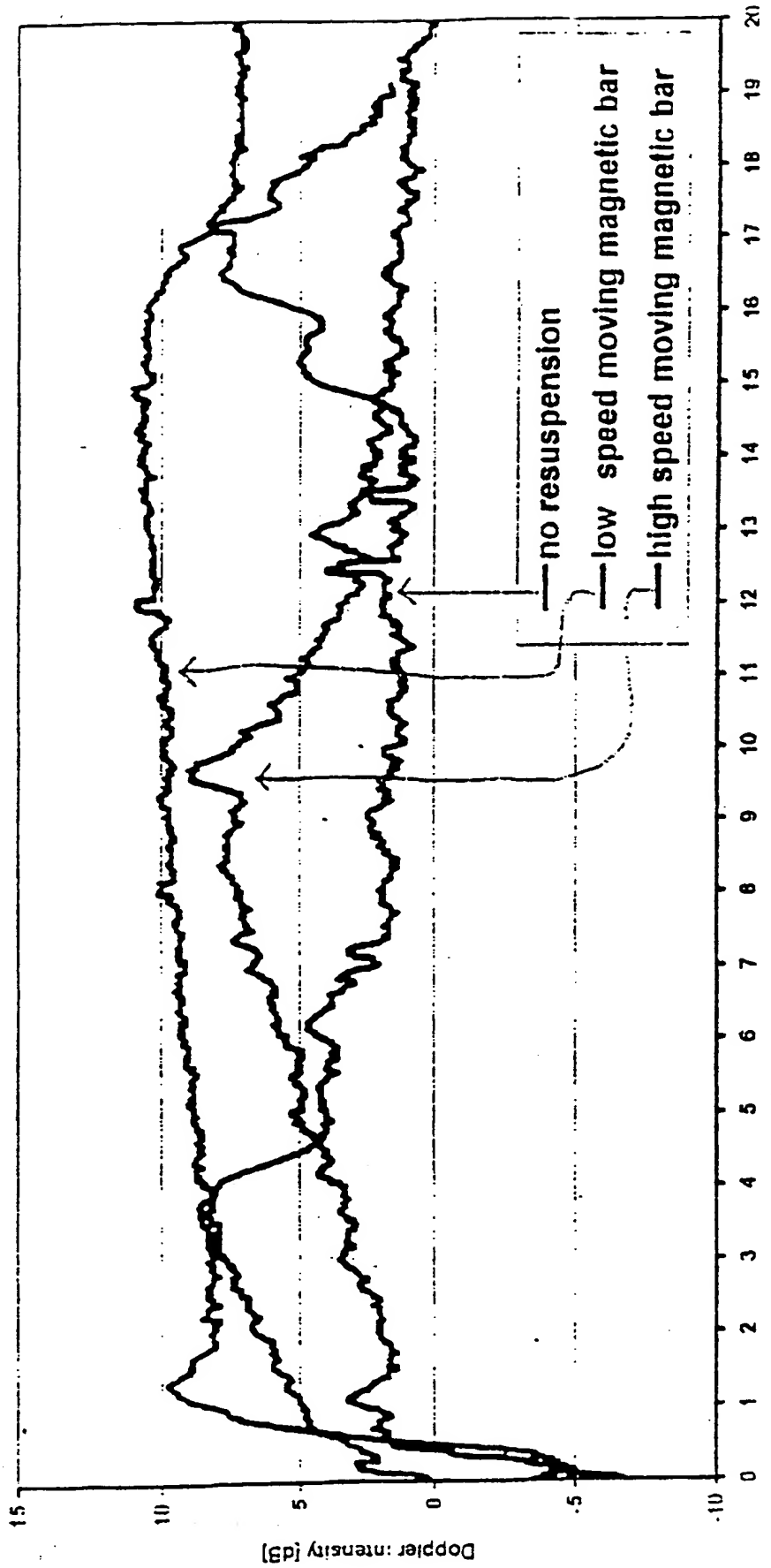
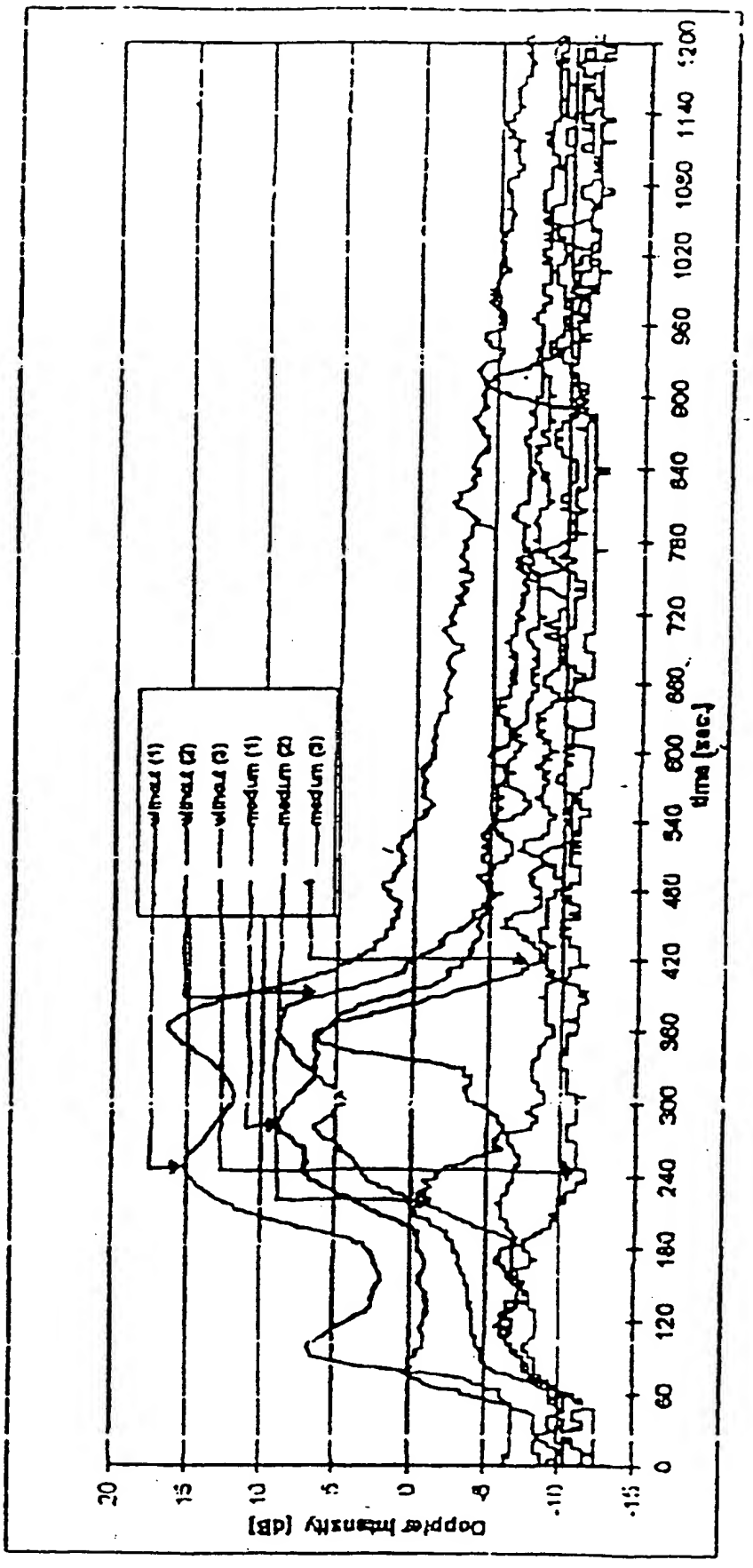

no resuspension
low speed moving magnetic bar
high speed moving magnetic bar
time [min.]
Doppler intensity [dB]

Figure 5


Doppler intensity [dB]
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10
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0
-5
-10
-15
0
60
120
180
240
300
360
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480
540
600
660
720
780
840
900
960
1020
1080
1140
1200
time [sec.]
vitreal (1)
vitreal (2)
vitreal (3)
medium (1)
medium (2)
medium (3)

Figure 6

Q2

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
51622BWOM1X00-P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/06290	26/08/1999	28/08/1998
Applicant		
SCHERING AKTIENGESELLSCHAFT et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [ ] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. 1

   [ ] as suggested by the applicant.

   [X] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

In ...ional Application No
PCT/EP 99/06290

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61M5/145 B01F11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61M B01F

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 687 000 A (EISENHARDT ANNE R ET AL) 18 August 1987 (1987-08-18) abstract; figures	1,4-6
X	US 5 352 036 A (HABER TERRY M ET AL) 4 October 1994 (1994-10-04) abstract; figures	1,4-6, 13,14
X	US 3 789 670 A (ROSENWALD G) 5 February 1974 (1974-02-05) column 3, line 35 - line 36; figures -/—	1,4,5,7, 8,12-15, 17,20, 21,23, 24, 27-30, 32,33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
23 December 1999	11/01/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

In ional Application No
PCT/EP 99/06290

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